pointed out by the Examiner. However, the Applicant has the following comments.

In claim 1, the Examiner stated that there was no antecedent basis for "the osmolarity," "the form" or "the resistance." The Examiner also stated that there was no antecedent basis for "the osmolarity" or "the form" in claim 12. MPEP § 2173.05(e) states that a claim is indefinite when it contains words or phrases whose meaning is unclear. This section also states that "[O]bviously, however, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite." Applicant submits that "the osmolarity" and "the form" in claims 1 and 12 and "the resistance" in claim 1 are not indefinite. Applicant submits none of these words render these claims unclear and that the scope of these claims would be readily ascertainable by one of ordinary skill in the art. In claim 9, applicant submits that there is sufficient antecedent basis for "the parameters" in claim 1.

In view of the amendments and arguments to claims 1-3, 8-9, 12-14 and 19, the rejection of claims 1-21 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claims 1-21 were rejected under 35 U.S.C. § 102(e) as being anticipated by Lloyd et al. (U.S. Patent 5,660,166). Applicant respectfully traverses this rejection.

The present invention is based upon the discovery that dry dispersible powders can be used to alter the osmolarity of airway surface liquids provided

that an effective amount of a substance capable of affecting osmolarity is inhaled by a subject. Blood and other body fluids typically have a steady state osmolarity which is shared by the airway surface liquid. Osmolarity of this liquid may be increased, for example, by exercise, which drives off water. When this occurs, the blood supply compensates by diluting the remaining liquid. Saline has the same osmolarity as body fluids and is used as a carrier or diluent for inhalation because it preserves the osmolarity of the airway surface fluid unchanged.

The above-identified application describes a wet aerosol test that uses a hyper-osmolar saline in order to deliberately change in the osmolarity of the airway surface liquid. The discovery the inventor made is that dry powders, in particular, mineral salts, sugars and sugar alcohols, in sufficient quantity, can also be used to alter osmolarity.

The Examiner states that Lloyd et al. disclose the use of dry powder compounds to be inhaled by the patient. Applicant submits that this is not correct. Lloyd et al. disclose a system for intrapulmonary delivery of aerosolized aqueous formulations. Preferably, formulations are low viscosity liquid formulations which can be easily aerosolized to produce aerosol droplets having a diameter of between 0.5 and 12 microns. Lloyd et al. does mention the use of dried powders, however, these powders must be dissolved in a liquid prior to aerosolization. For example, in column 5, lines 65-67 in Lloyd et al. states, "[A]nother advantage is that drugs which are unstable in a liquid (e.g. aqueous)

state can be stored in a dry state and combined with a liquid immediately prior to aerosolization." Additionally, Column 9, lines 4-19 state:

> The contents of each container preferably consists essentially of a liquid, flowable formulation which includes a pharmaceutically active drug of any type and (if the drug is not liquid and of a sufficient low viscosity to allow the drug to be aerosolized) an excipient carrier, i.e., preferably without any additional material such as preservatives which might affect the patient. The formulation is a liquid, flowable formulation with a relatively low viscosity that can be readily aerosolized and is more preferably a flowable, liquid formulation consisting essentially of a pharmaceutically active drug dissolved or dispersed in an excipient carrier. When the contents must be stored in a dry state, the package further includes another container which holds the liquid and can be combined with the drug immediately prior to administration by breaking a rupturable membrane separating the container (emphasis added).

Finally, column 17, lines 6-14 state:

> The drug formulation is preferably in a low viscosity liquid formulation which is most preferably a formulation which can be aerosolized easily and includes respiratory drug formulations currently used in neutralizers. The viscosity of the drug by itself or in combination with a carrier must be sufficiently low so that the formulation can be forced through the membrane 14 to form an aerosol, e.g., using 20 to 200 psi to form an aerosol preferably having a particle size in the range of about 0.5 to 12 microns (emphasis added).

Therefore, Lloyd et al. simply do not disclose a method of provoking the narrowing of an airway or increasing the mucociliary clearance or inducing sputum by having a subject inhale into this or her airways a substance that is capable of altering the osmolarity of airway surface liquid, where the substance is in the form of a dispersible dry powder. Therefore, the rejection of claims 1-21 as being anticipated by Lloyd et al. under 35 U.S.C. § 102(e) should be withdrawn.

Claims 1-9 and 12-19 were rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Anderson et al. (U.S. Patent 5,642,728). Applicant respectfully traverses this rejection.

Anderson et al. discloses the administration of a pharmaceutically active compound for the treatment of disease by means of a dry powder inhaler device which can be used to deliver a large proportion of the powder in the form of particles having a diameter of less than 10 microns.

Figure 2 in Anderson et al. shows the clinical effect of various cumulative metered doses of salbutanol inhaled from a dry powder inhaler system as described in the specification. Figure 3 of Anderson et al. show a graph comparing the mean values of FEV_1 (L) in percent of mean baseline, representing clinical effect, in patients given various cumulative, metered doses of salbutanol via MDI or a dry powder inhaler system as described by Anderson et al.

Cumulatively, both Figures 2 and 3 of Anderson et al. demonstrate an FEV_1, which correlates with an important in lung function.

This is marked contrast to the present invention. In the present invention, the dry powder is used to narrow the airways. This is demonstrated in Figure 1 of the present invention which demonstrates a fall in FEV_1.

The examples of Anderson et al. demonstrate that the drug is given to a subject in concentrations that are suitable for achieving clinical effectiveness. Thereupon, the delivery of the drug in Anderson et al. results in a physiological effect in the patient. Anderson et al. simply do not disclose the inhalation of a dry powder in a sufficient quantity to cause a change in the <u>osmolarity</u> of the

airway surface liquid in the patient. Such a change is a physicochemical change and not a physiological change.

Additionally, Anderson et al. also disclose that inhalable expectorant drugs that have a physiological effect on the lungs also increase mucociliary clearance. As discussed earlier, this is a physiological effect; there is no alteration of the osmolarity of airway surface liquid because such an effect is a physicochemical effect.

Anderson et al. does disclose the use of substances such as mannitol, sucrose, etc. However, Anderson et al. states that these substances are simply to be used as additives such as diluents and carrier substances.

Anderson et al. further state that "[A]ny inhalable pharmaceutically active compound which can be formulated into a powder with the appropriate physicochemical, pharmaceutical, and powder characteristics, as these characteristics are recognized in the art, iks suitable for use in the present invention" (column 3, lines 66-67 - column 4, lines 1-2). Applicant submits that appropriate characteristics recognized in the art are that the inhaled powder should be in a quantity that causes it to have iso-osmolar characteristics so that there is no change in osmolarity of the airway surfaces to complicate the clinical effect of the drug.

Therefore, Anderson et al. simply do not disclose a method of provoking the narrowing of an airway or increasing the mucociliary clearance or inducing sputum by altering the osmolarity of the airway surface liquid in a patient by having the patient inhale a dispersible, dry powder. Therefore, the rejection of

claims 1-9 and 12-19 are being anticipated by Anderson et al. under 35 U.S.C. § 102(e) should be withdrawn.

Claims 10-11 and 20-21 were rejected under 35 U.S.C. § 103(a) as being obvious over Anderson et al. in view of Lloyd et al.

Claims 10-11 and 20-21 are dependent claims and therefore incorporate the limitations for which they depend. Claim 10 is dependent for claim 1 and claim 11 is dependent from claim 10. Claim 20 is dependent from claim 12 and claim 21 is dependent from claim 20.

As discussed earlier with respect to the 35 U.S.C. § 102(e) rejection neither Lloyd et al. nor Anderson et al. disclose or suggest a method of provoking the narrowing of an airway or increasing the mucociliary clearance or inducing sputum by altering the osmolarity of the airway surface liquid in a patient by having the patient inhale a dispersible, dry powder. Therefore, this rejection should be removed.

Finally, in response to the Notice of Draftspersons Patent Drawing Review, enclosed herewith are corrected drawings 1-4.

In view of the foregoing amendments and arguments, Applicant submits that claims 1-21 are now in condition for allowance.

If any fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account number 04-1644.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that the attached Amendment is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on December 11, 1997.

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